

Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy

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Introduction

Hypertrophic Cardiomyopathy (HCM) is the most frequent genetically transmitted cardiomyopathy, affecting one in every 500 people in the United States¹, caused by dominant genetic mutations in genes encoding contractile proteins of the sarcomere or adjacent Z disc², whose condition may start from childhood to senility. Although HCM is a complex and heterogeneous disease with various categories of clinical outcomes, the most important complication related to it is sudden death, with an incidence of 1%–3% per year in patients with the disease, usually asymptomatic until the event² especially in young people under the age of 30. In fact, the HCM is a major cause of sudden death in athletes in the United States³.

The analysis of the data retrieved from defibrillators and implantable pacemakers in patients with HCM demonstrates that the mechanism of sudden death is ventricular tachycardia, followed by ventricular fibrillation⁴. Cardiac structural changes resulting from HCM such as cellular disorganization (misaligned myocytes), fibrosis and cell death are the most probable causes of arrhythmias.

There is not an isolated test identifying with a reasonable degree of accuracy those patients at risk of sudden death, which makes stratification complex and imprecise. A study in patients with HCM who underwent routine 24-hour Holter⁵ showed that 90% of patients had ventricular arrhythmias, and more than 20% had ventricular extrasystoles higher than 200/24h; more than 40% had paired ventricular extrasystoles; and perhaps the most important finding in the study, 20% to 30% of patients had non-sustained ventricular tachycardia. This high prevalence of ventricular arrhythmias on Holter is certainly disproportionate to the relatively low incidence of sudden death in patients with HCM², clearly emphasizing its low accuracy in stratifying these patients.

Basic technical aspects of Cardiac MRI (CMRI)

Cardiac magnetic resonance imaging (CMRI) is a noninvasive test that does not require the use of ionizing radiation. It is capable of phenotyping the heart muscle in about 30 minutes in a detailed and accurately manner. In fact, the CMRI is now the standard noninvasive reference

for determining systolic function (global and regional), cavity volumes, mass, thickness and fibrosis/myocardial viability^{6,7}.

To perform the CMRI, the patient enters a powerful magnet (at least 1.5 tesla — “open” magnets have a very small field and are not usually suitable for CMRI), which is capable of producing images on any plane in the body. The sequences commonly used are cine (function evaluation, cavity volumes etc.), T1 or T2-weighted anatomical sequences (static evaluation of masses, for example), perfusion imaging (to assess myocardial perfusion and mass perfusion) and late enhancement (to assess myocardial fibrosis).

Late enhancement is perhaps the biggest distinguishing feature of MRI, because no other method shows myocardial fibrosis directly and noninvasively. Late enhancement is widely used to evaluate cardiomyopathies. HCM is one of the conditions that most benefit from this technique. In short, late enhancement is performed after injection of gadolinium-based contrast by sequences that cancel normal myocardial signal, enhancing the myocardium with gadolinium. As the normal myocardium is compact and has only 25% of extracellular matrix, it lacks gadolinium, which is an exclusively extracellular molecule. In the region of myocardial fibrosis, there is a marked increase in the extracellular matrix, especially from the collagen deposition, which leads to sharp increase in concentration (or, technically speaking, in distribution volume) of gadolinium, appearing on the images with higher signal intensity, usually white or light gray. The fibrosis revealed by late enhancement may form ventricular arrhythmia reentry circuit.

MRI in the diagnosis of HCM

The phenotypical diagnosis of HCM is delivered upon detection of muscle thickness equal or greater than 1.5 cm in any myocardial segment in patients in whom we would not expect this finding (patients without hypertension or aortic stenosis)⁸.

This “magic number,” however, should be used with caution, because, for example, in a patient weighing 50 kg and wall thickness of 0.7 cm, the finding of a 1.3 cm segment is highly suggestive of the disease. The differential diagnosis of HCM should be delivered with other diseases that result in hypertrophy, such as Fabry and Danon, but it should be taken into account that the latter are far rarer than HCM.

Echocardiography has limitations for diagnosis of HCM. The main limitation is related to unfavorable acoustic windows and technical limitations of the method, such as difficulties in viewing the LV apex and precise epicardial limits on the sidewall (due to its close contact with the air present in the lungs). This results in false-negative cases and underestimation of higher myocardial thickness^{9,10}. Apical aneurysms, which, although infrequent, have prognostic significance, also have their viewing and characterization limited on echocardiogram¹¹ (Figure 7).

Keywords

Hypertrophic cardiomyopathy; Magnetic resonance spectroscopy/diagnostic use; Cardiac arrhythmias.

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CMRI is currently the reference standard for the phenotypical diagnosis of HCM, since it does not present acoustic window limitations; it has an excellent spatial resolution and the ability to show myocardial fibrosis (Figure 1).

Differentiation of HCM and Hypertensive Heart Disease on CMRI

Hypertension is a highly prevalent disease (estimated at more than 30% of the adult population in Brazil¹²) and, obviously, even hypertensive patients may have HCM. Therefore, the exclusion of hypertension as a diagnostic criterion for HCM is problematic. Although there is no definitive answer to this question, some factors indicate more one disease than the other, such as highly asymmetrical hypertrophy or apical hypertrophy, indicating more HCM than hypertensive heart disease.

Another lesser known aspect that may differentiate the two is the presence of fibrosis. It is well established that both hypertensive heart disease and HCM result in myocardial fibrosis that can be viewed by late enhancement on CMRI. But an interesting histopathological study¹³ revealed that whereas patients with hypertensive heart disease had a fourfold increase in the extracellular volume compared to controls (due to fibrosis), patients with HCM had a 17-fold increase. This study corroborated by another study showing three to four times increase in the volume of late enhancement on HCM compared to hypertensive heart disease and aortic stenosis¹⁴.

Therefore, it is expected that significant findings of myocardial fibrosis by late enhancement or severe increase in extracellular volume be more suggestive of HCM, although there is no specific cut-off point yet.

Late enhancement and cardiac events in HCM

As it was said, it is particularly difficult to stratify the risk of sudden death in patients with HCM — there is no method (not even genetic studies) with reasonable accuracy to allow its isolated use in risk stratification. In this context, though still imperfect, CMRI seems to outperform the others.

Recent studies evaluate CMRI for predicting cardiac events in patients with HCM¹⁵⁻¹⁷. In the first of them¹⁶, with 220 patients and mean follow-up of approximately three years, the authors assessed cardiovascular mortality as an outcome, and reported that none of the variables commonly used for risk stratification (maximum myocardial thickness, obstruction of the LV outflow tract, history spontaneous ventricular tachycardia or syncope and a family history of sudden death) was significantly associated with cardiovascular mortality when adjusted in multivariable analysis including fibrosis on CMRI (late enhancement). In fact, even after adjusting for all the above variables, the presence of late enhancement had an odds ratio of 8.01, i.e., determined 700% increase in risk of cardiovascular death.

The second study included 217 patients with HCM and followed them up for about three years on average¹⁷. The authors present results similar to the first one, i.e., presence of late enhancement was predictive of cardiac

outcomes, even after adjustment for usual risk factors for sudden death in HCM. Another study demonstrated that the presence of fibrosis 18g or 15% of LV mass was significantly associated with ventricular arrhythmias¹⁸.

Nevertheless, one variable must be taken into consideration before using late enhancement for the clinical indication of defibrillators: approximately 70% of patients with phenotype of HCM have some degree of late enhancement¹⁴ — considering that the average mortality of patients with HCM is 1% to 3% per year, we will be certainly unnecessarily implanting defibrillators in various patients with enhancement.

Both studies evaluated the extent of enhancement (in contrast to the binary information yes/no) and found that the greater the degree of fibrosis, worse the outcomes. Hence, not only the presence or absence of late enhancement, but also the extent of fibrosis (albeit subjectively) should be part in the treatment decision (Figures 2, 3 and 4). Another very useful information in clinical practice is that patients without late enhancement showed no cardiovascular death in both studies. That is, late enhancement is perhaps more useful for its negative predictive value than for its positive value to identify patients at risk of sudden death.

Obstruction of Left Ventricular outflow and mitral insufficiency

Patients with marked hypertrophy and reduced ventricular cavity may present, during systole, a phenomenon of dynamic obstruction of the flow between the Left Ventricle (LV) and the aorta. Systolic narrowing of Left Ventricular outflow tract (LVOT) leads to an increase in the speed of ejection flow, which, associated with redundant mitral leaflets and forward positioning in these patients produces a suction effect of the mitral valve and its subvalvular apparatus, which in turn increases obstruction even more¹⁹. The detection of this phenomenon and the establishment of its severity are essential for clinical management. Although echocardiography is the reference complementary test in this context, both the increase in subvalvular gradient and Systolic Anterior Motion (SAM) of the mitral valve can be easily viewed and even quantified on Magnetic Resonance Imaging (MRI).

The SAM described here also impairs the coaptation of the mitral valve leaflets leading to regurgitation. In some cases, valve failure may be severe and determinant in the clinical presentation. Cine sequences and other sequences designed to quantify flow and gradients are used in these cases to determine not only the severity of mitral regurgitation, but also to confirm its mechanism (Figure 5). For example, a regurgitant jet not directed posterolaterally should raise suspicion of another cause for regurgitation than SAM alone.

Future Directions — MRI in preclinical evaluation of HCM

A recent study published in the New England Journal of Medicine²⁰ had a major impact on the understanding of HCM. The authors studied exhaustively three groups of people: a) controls; b) phenotype HCM + and genotype + and; c) phenotype HCM - and genotype +. They found

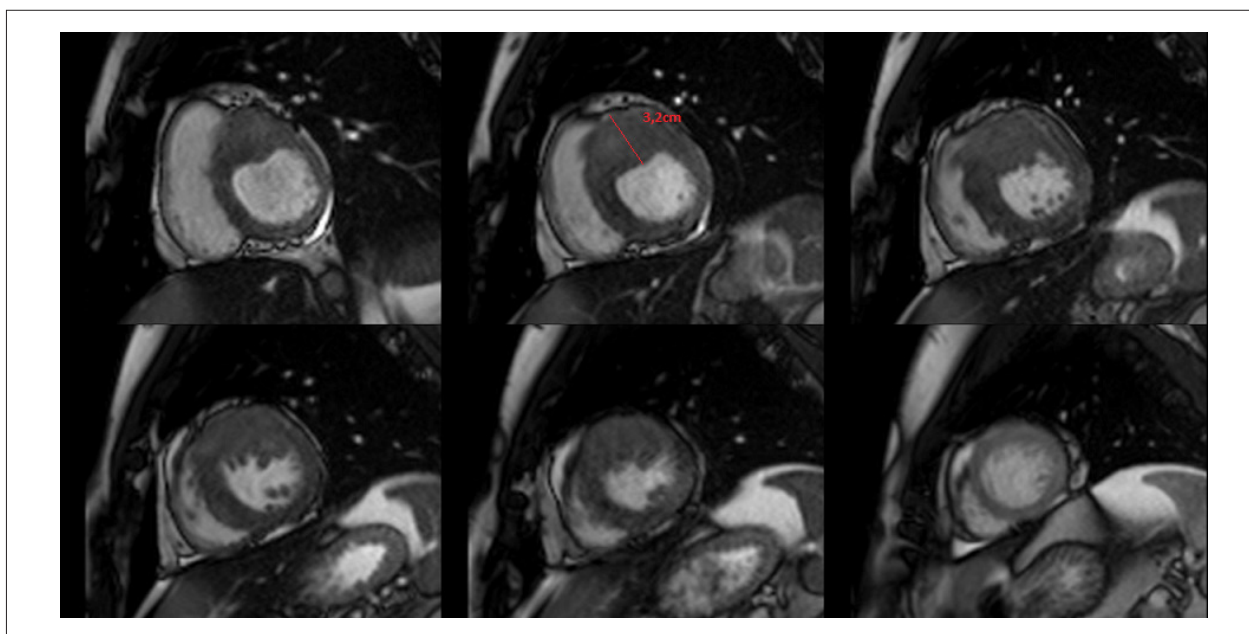


Figure 1 – Patient aged 40 with abnormalities on electrocardiogram consistent with left ventricular hypertrophy and no wall hypertrophy on echocardiography. Short-axis cine images of the heart reveal severe anterior anteroseptal asymmetric hypertrophy with increased wall thickness of 3.2 cm, consistent with HCM.

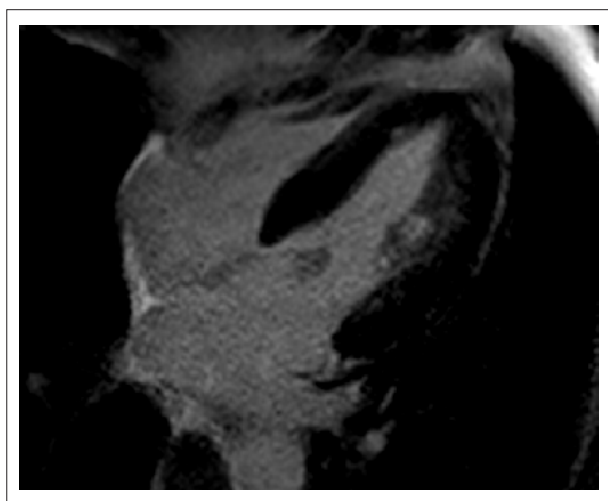


Figure 2 – Four-chamber long axis after contrast injection in patients with HCM without late enhancement.

that, compared to controls, HCM patients with ventricular hypertrophy (positive phenotype) had markedly increased levels of collagen deposition markers (a marker that suggests active fibrosing process) — but the most striking findings are those which showed that patients with the HCM gene but without any ventricular hypertrophy also had increased levels of these markers of collagen deposition (albeit lower than patients with positive phenotype). This indicates that the process of fibrosis precedes hypertrophy, indicating that hypertrophy is secondary to fibrosis, not the opposite, as it was usually believed to be

the case. That is, HCM seems to be a fibrosing disease before hypertrophy, or hypertrophy may be reactive.

Viewing myocardial fibrosis by the late enhancement technique revolutionized our understanding of cardiomyopathies, but it has limitations. The main one is that, for enhancement to occur, there must be coalescing fibrosis, in contrast to normal myocardium. If there was diffuse increase in collagen deposition, it would not be possible to view it. So far, a new MR sequence has been recently developed to allow the absolute quantification of the T1 time of cardiac tissues (map T1), from which, using a mathematical calculation that considers the patient's hematocrite, the myocardial extracellular volume can be determined²¹. This technique would detect the increase in myocardial collagen even before any hypertrophy. Further studies underway with the T1 map and calculation of extracellular volume of patients with HCM should better explain the role of this new technology in clinical management (Figure 6).

Conclusions

The CMRI is a fundamental tool in the management of patients with HCM. It has proven to be more accurate than transthoracic echocardiography in the diagnosis and quantification of wall thickness, and enables evaluation of HCM complications, such as apical aneurysms and mitral regurgitation. The CMRI is the only noninvasive test that can provide information on myocardial fibrosis, which seems to be the best predictor of sudden death in HCM, and its absence has an excellent negative predictive value for sudden death in these patients. The T1 map with estimated myocardial extracellular volume is a promising technique for earlier disease detection and better quantification of risk.

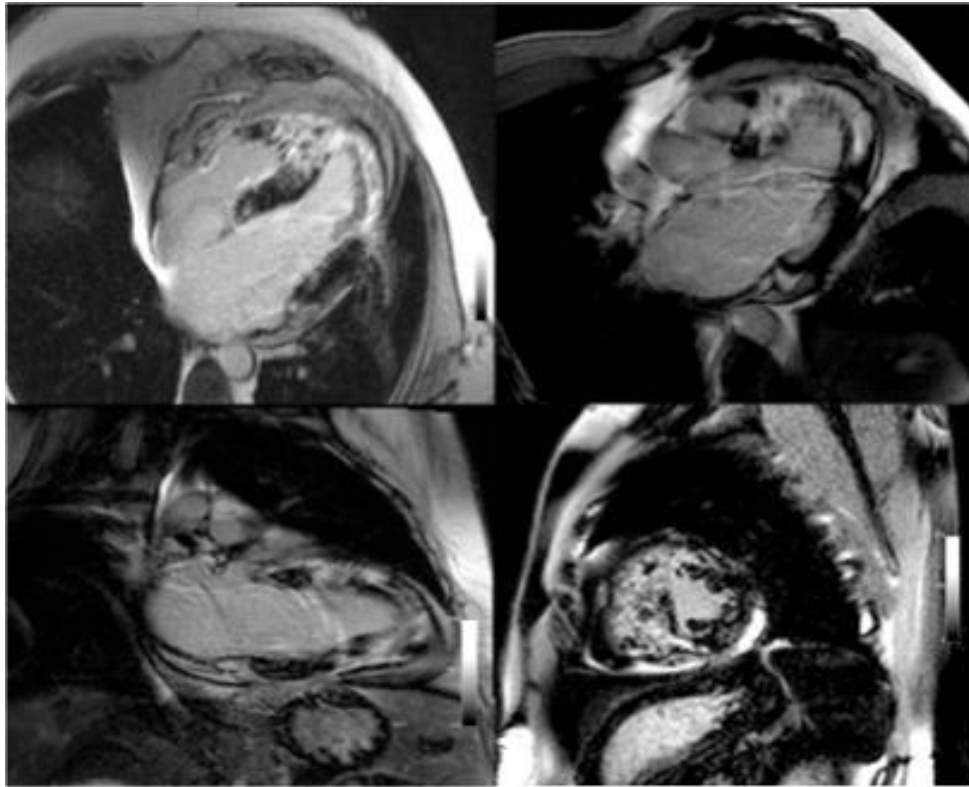


Figure 3 – Long and short-axis late enhancement images of the heart with extensive fibrosis (white areas in contrast with “healthy” myocardium in black), involving the right ventricle.

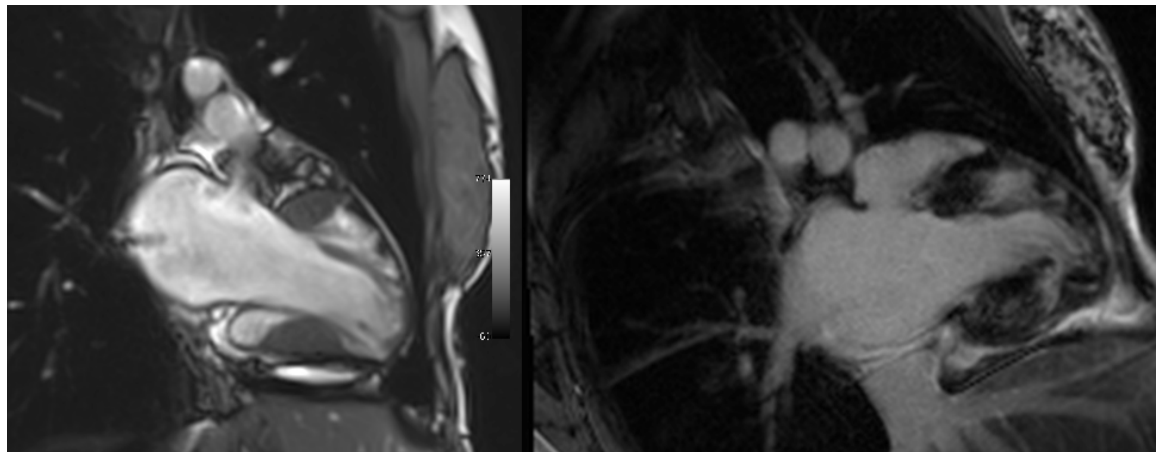


Figure 4 – Two-chamber long axis cine imaging (left) and late enhancement (right) of 21-year-old female patient with left ventricular deformity due to asymmetric myocardial hypertrophy interspersed with narrowed myocardial areas. There is also marked left atrial enlargement and presence of late enhancement in hypertrophic areas.

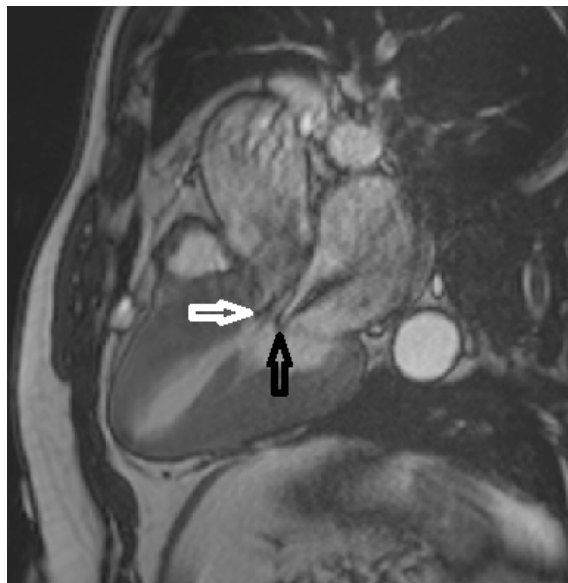


Figure 5 – Left ventricular three-chamber long axis cine imaging showing asymmetric septal HCM with obstruction of the left ventricular outflow tract (black arrow), mitral systolic anterior motion (white arrow) and mitral regurgitation.

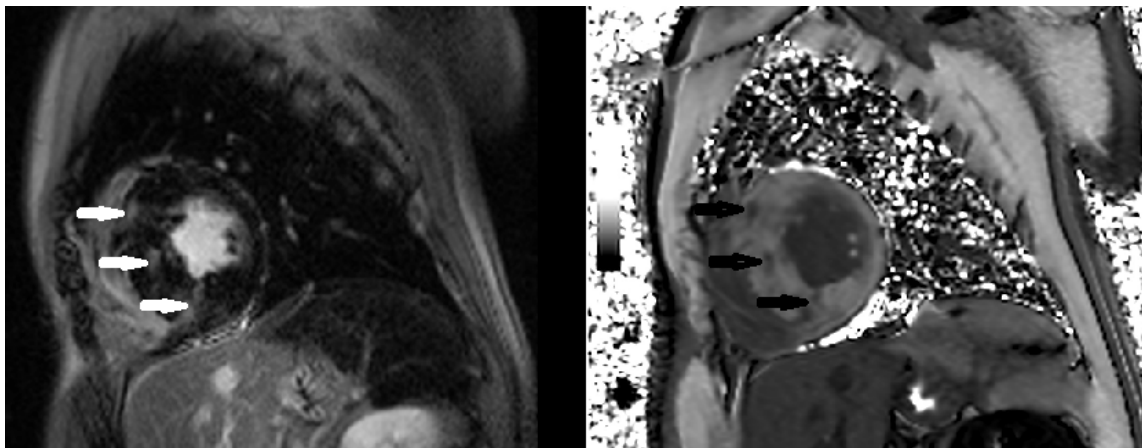


Figure 6 – Short axis of the heart of patient with asymmetric septal HCM evaluated by late enhancement (on the left) and T1 map (right image). Areas of fibrosis appearing in late enhancement images as regions of higher signal intensity (white arrows) in the middle of the normal narrowed myocardium corresponding to regions with low signal intensity (black arrows) on the T1 map. The extracellular volume measured in the septum was calculated at 42% (normal up to 30%).

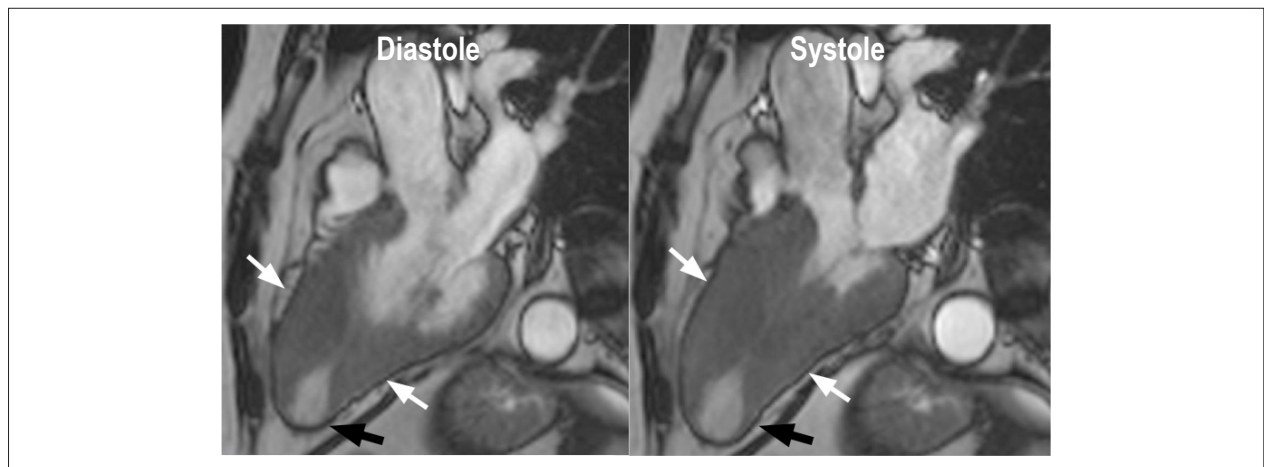


Figure 7 – Three-chamber long axis section of patient with hypertrophic cardiomyopathy with medioventricular prevalence, determining subaortic gradient (white arrows). Apical dyskinesia aneurysm (black arrow) is also observed.

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